FOREWORD INTRODUCTION

2,4-DICHLORONITROBENZENE

CAS N°: 611-06-3

SIDS Initial Assessment Report

For

SIAM 4

Tokyo, Japan, 20-22 May 1996

1. Chemical Name:	2,4-Dichloronitrobenzene
2. CAS Number:	611-06-3
3. Sponsor Country:	Japan
	National SIDS Contact Point in Sponsor Country: Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs, Japan
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	As a high priority chemical for initial assessment, 2,4-dichloronitrobenzene was selected in the framework of the OECDHPV Chemicals Programme. SIDS Dossier and Testing Plan were reviewed at a SIDS Review Meeting in 1994, where the following SIDS Testing Plan was agreed: The original report was already circulated in March 1996, and the report was revised according to the comments from member countries.

No testing	( )
Testing(X)	Physical-Chemical Properties
	Vapour pressure
	Partition coefficient
	Water solubility

Environmental fate/Biodegradation

Biodegradation

Photodegradation

Stability in water

Ecotoxicity

Acute toxicity to fish

Acute toxicity to daphnids

Toxicity to algae

Chronic toxicity to daphnids

Toxicity

Repeated dose toxicity

Reproductive/developmental toxicity

Chromosomal aberration in vitro

At SIAM-4, the conclusion was approved with comments.

Comments at SIAM-4: Rearrangement of the documents.

7. Review Process Prior to the SIAM:

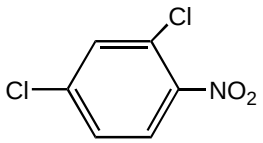
8. Quality check process:

9. Date of Submission: Date of Circulation: 30 April 1996

10. Date of last Update:

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	611-06-3
Chemical Name	Benzene, 2,4-dichloro-1-nitro-
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

A potential hazard to the environment due to toxicity to daphnids is identified, but exposure is low in the sponsor country.

Unless further information on exposure in other Member countries presents evidence to the contrary, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of 2,4-dichloronitrobenzene in Japan was less than 50 tonnes during 1990 - 1993, and 1,500 tonnes in Germany in 1990. This chemical is used as an intermediate for the synthesis of pigments, pesticides and medicinal drugs in industry in Japan. This chemical is stable in neutral, acidic or alkaline solutions, and is considered as “not readily biodegradable”.

The potential environmental distribution of 2,4-dichloronitrobenzene obtained from a generic fugacity model (Mackay level III) showed that the chemical will be distributed mainly to water and soil. The predicted environmental concentration (PEC_{local}) of this chemical was estimated to be 2.7 x 10^{-8} mg/l from a Japanese local exposure scenario.

For the environment, various NOEC and LC_{50} values were gained from test results; LC_{50} = 13 - 21 mg/l (acute fish); EC_{50} = 12 mg/l (acute daphnia); EC_{50} = 2.0 mg/l (acute algae); NOEC = 1.8 mg/l (algae); NOEC = 0.056 mg/l (long-term daphnia reproduction). The lowest chronic toxicity result, 21d-NOEC (reproduction) of *Daphnia magna* (0.056 mg/l), was adopted for the calculation of the PNEC. The assessment factor of 100 was used to both acute and chronic toxicity data to determine PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the PNEC of the chemical is 0.00056 mg/l in the present report. The PEC is lower than the PNEC, therefore the environmental risk is presumably low.

2,4-Dichloronitrobenzene is produced in a closed system and is used as an intermediate in industry. As this chemical is not taken out from the vessel, the only situation that could lead to occupational exposure is when workers maintain the reaction vessel under local exhaust ventilation. Although there is no actual exposure data, using the physical-chemical properties of the substance and the EUSES model, exposure levels were calculated as 0 - 0.1 ppm for inhalation and 0 - 0.1 mg/cm^2/day for the dermal route. However workers wear personal protective equipment (e.g. chemical cartridge respirator with an organic vapour cartridge) during the filling process. Therefore, the exposure at the work place is considered to be negligible for the current situation. In addition, this chemical is not contained in consumer products, because it is an intermediate in industrial use. As for indirect exposure via the environment, PEC_{local} in surface water was estimated to be 2.7 x 10^{-8} mg/l from a local exposure scenario. The concentration in drinking water is estimated to be less than 2.7 x 10^{-8} mg/l (corresponding to a daily dose of less that 9 x 10^{-10} mg/kg/day).

Although a positive result was obtained from an Ames test, the chemical showed no genotoxic effect in a chromosomal aberration test *in vitro*. In an OECD combined repeated dose and reproductive/developmental toxicity test, moderate effects to liver (e.g. increased liver weight and necrosis) and kidney (e.g. increased kidney weight and

basophilic changes in the renal tubules) were observed at the middle dose (40 mg/kg/day). Similar slight effects to the kidney were also seen in females at the lowest dose (8 mg/kg/day). Therefore, NOEL was strictly considered to be less than 8 mg/kg/day. Regarding reproductive/developmental toxicity, the chemical did not show any effects on mating fertility or estrous cycle. However, all pups of two females were stillborn, and during the lactation period, pups of three females died at the highest dose (200 mg/kg/day). In addition, functional disturbances in delivery or lactation caused by the test substance was expected. The NOEL for reproductive toxicity was 40 mg/kg/day.

Regarding indirect exposure via environment, the daily intake through drinking water is estimated to be less than 9.0 x 10^{-10} mg/kg/day. For human health, although NOEL is estimated as less than 8 mg/kg/day for repeated dose and 40 mg/kg/day for reproductive toxicity, the margin of safety is very large. Therefore, health risk through the environment, in general, is considered to be presumably low due to its use pattern and exposure situation.

In conclusion, no further testing is needed at present considering its toxicity and exposure levels.

NATURE OF FURTHER WORK RECOMMENDED

FULL SIDS SUMMARY

CAS NO: 611-06-3		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			29-31 °C
2.2	Boiling Point			258 °C (at 1013 hPa)
2.3	Density			1.54 at 15 °C
2.4	Vapour Pressure		OECD TG 104	1.0 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	2.90 at 25 °C
2.6 A.	Water Solubility		OECD TG 105	200 mg/L at 25 °C
B.	pH			No data available.
	pKa			Not observed.
2.12	Oxidation: Reduction Potential			No data available.
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Estimation	Half-life: 7.90 x 10^{-2} years (direct photolysis in water)
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4.0, 7.0 and 9.0
3.2	Monitoring Data			Not detected in Japan in 1994
3.3	Transport and Distribution		Calculated (Fugacity level III model)	If released 100% to water: In Air: 0.80 % In Water: 91.79 % In Soil: 5.28 % In Sediment: 2.13 %
3.5	Biodegradation		OECD TG 301C	Not readily biodegradable: 0 % (BOD) in 28 days, 4-6 % (HPLC) in 28 days.
3.6	Bioaccumulation		Unknown	BCF: 118
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (72hr): 18 mg/L LC_{50} (96hr): 13 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (24hr): 12 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72hr): 2.0 mg/l NOEC: 1.8 mg/l

CAS NO: 611-06-3		SPECIES	PROTOCOL	RESULTS
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Immobility): > 0.56 mg/l EC_{50} (21d, Reproduction): 1.0 mg/l NOEC (21d, Repro): 0.056 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			No data available.
4.6.2	Toxicity to Terrestrial Plants			No data available.
(4.6.3)	Toxicity to Other Non- Mammalian Terrestrial Species (Including Birds)			No data available
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Unknown	LD_{50}: 990 mg/kg
5.1.2	Acute Inhalation Toxicity			No data available.
5.1.3	Acute Dermal Toxicity	Rabbit	Unknown	LD_{50}: 921 mg/kg
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	NOEL = < 8 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S.typhimurium*	Other method	Positive
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	CHL cells	OECD TG 473 and Japanese Guidelines	Negative (With and without metabolic activation)
5.6	Genetic Toxicity In Vivo			No data available.
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOEL Parental = 40 mg/kg/day NOEL F1 offspring = 40 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			
5.11	Experience with Human Exposure			

SIDS Initial Assessment Report

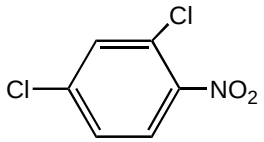
1 IDENTITY

1.1 Identification of the Substance

CAS Number: 611-06-3

IUPAC Name: Benzene, 2,4-dichloro-1-nitro-
Molecular Formula: $C_6H_3Cl_2NO_2$

Structural Formula:



Synonyms: 2,4-Dichloronitrobenzene

1.2 Purity/Impurities/Additives

Degree of Purity: > 93 %

Major Impurities: 2,6-Dichloronitrobenzene

Essential Additives: No additives

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value
Melting point	29-31 °C
Boiling point	258 °C
Vapour pressure	1.0 Pa at 25 °C
Water solubility	200 mg/l at 25 °C
Partition coefficient n-octanol/water (log value)	2.9

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The production volume of 2,4-dichloronitrobenzene in Japan was less than 50 tonnes/year in 1988-1992, and 1,500 tonnes/year in Germany in 1990. 2,4-Dichloronitrobenzene is not readily biodegradable (OECD 301C: 0 % degradation after 28 days). 2,4-Dichloronitrobenzene is not hydrolyzed at pH 4, 7 and 9. Direct photodegradation in water is expected, and its half-life is 4 weeks.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Global Exposure

The potential environmental distribution of 2,4-dichloronitrobenzene obtained from a generic level III fugacity model is shown in Table 2. The results show that if 2,4-dichloronitrobenzene is released mainly to air or soil, it is unlikely to distribute into other compartments. But, if 2,4-dichloronitrobenzene is released mainly to air, it is likely to be transported to soil.

Table 2: Environmental distribution 2,4-dichloronitrobenzene using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	12.07 %	0.80 %	0.12 %
Water	7.86 %	91.79 %	2.80 %
Soil	79.89 %	5.28 %	97.02 %
Sediment	0.18 %	2.13 %	0.06 %

Reference: EA & MITI, Japan (1994)

Local exposure

According to a Japanese manufacturer, 1.4 kg/y (estimated) of 2,4-Dichloronitrobenzene are released with 5.25 $x10^7$ t/y of effluent into a bay. Local predicted environmental concentration (PEC_{local}) is 2.7 x 10^{-8} mg/l, employing the following calculation model. In this case, the dilution factor is estimated to be 1000.

$$\frac{\text{Amount of release } (1.4 \times 10^6 \text{ mg/y})}{\text{Volume of effluent } (5.25 \times 10^{10} \text{ l/y}) \times \text{Dilution factor } (1000)}$$

2.2.2 Photodegradation

The half-life time of 7.90 x 10^{-2} years is estimated for the degradation of 2,4-dichloronitrobenzene in water by direct photodegradation (Lyman et al., 1981).

2.2.3 Stability in Water

The chemical is stable in water at pH 4, 7 and 9 (OECD TG 111).

2.2.4 Biodegradation

If released into water, this substance is not readily biodegraded (MITI (I), corresponding to the OECD 301C: 0 % degradation during 28 days based on BOD and 4 - 6 % based on HPLC analysis).

2.2.5 Bioaccumulation

A measured BCF of 118 in *Salmo gairdneri* (36 days) suggests that the potential for bioconcentration in aquatic organisms is low.

2.3 Human Exposure

2.3.1 Occupational Exposure

2,4-Dichloronitrobenzene is produced in a closed system and is used as an intermediate for the synthesis of medical drugs, pesticides and pigments. This substance is not taken out from the vessel. The only step that could lead to occupational exposure is maintaining of the reaction vessel under local exhaust ventilation. Workers wear protective eyeglasses, chemical cartridge respirator and rubber gloves during the maintaining process. Therefore, the exposure is expected to be negligibly small for the current situation.

Exposure levels calculated by the EU Exposure model, using physical-chemical data and the information above, are as follows:

At a production site of this chemical, exposure level could be estimated as:

Inhalation: 0 –0.1 ppm

Dermal: 0 –0.1 $mg/cm^2/day$

There is no actual measurement data of exposure. By wearing glasses, chemical cartridge respirator and rubber gloves during the maintenance process, the exposure level can be very low.

2.3.2 Consumer Exposure

2,4-Dichloronitrobenzene is not contained in consumer products, because 2,4-Dichloronitrobenzene is an intermediate for medicinal drugs, pesticides and pigments.

2.3.3 Exposure via the environment

The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. Based on the physical chemical properties of 2,4-Dichloronitrobenzene, a significant removal of during processing is not expected. Although PEC_{global} is not estimated, the concentration in drinking water is assumed to be less than 2.7×10^{-8} mg/l. This would correspond to a daily dose for humans of less than 9×10^{-10} mg/kg/day.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Acute Toxicity

The LD_{50} for acute oral and acute dermal toxicity in rats were reported as 990 mg/kg and 921 mg/kg, respectively. No result regarding inhalation toxicity was available.

3.1.2 Repeated Dose Toxicity

There is only one key study on repeated dose toxicity of 2,4-dichloronitrobenzene. This chemical was studied for oral toxicity in rats according to the combined repeated dose and reproductive/developmental toxicity test [OECD TG 422]. As the study was well controlled and conducted under GLP, this was appropriate to be regarded as a key study. Male and female SD rats were orally administered (gavage) at doses of 0, 8, 40 and 200 mg/kg/day.

One female rat given 200 mg/kg died during delivery, but no abnormal clinical signs were observed. The body weight gain of females given 200 mg/kg was lower than that of controls during the gestation period. Hematological examination revealed decreases in red blood cells in males given 8 mg/kg or more groups, decreases in hematocrit and hemoglobin, increases in reticulocytes, and alight anemia in males given 40 and 200 mg/kg. Blood clinical examination revealed increases total protein, albumin and gamma-GTP, and decreases in creatinine in males given 40 and 200 mg/kg. Total bilirubin and A/G ratio were increased in males given 200 mg/kg. Absolute and relative liver and kidney weights showed increase in both sexes given 200 mg/kg. Necropsy revealed enlargement of the liver in both sexes given 200 mg/kg, and enlargement of the kidneys in male 200 mg/kg group. Other treatment related gross findings included atrophy of the thymus and enlargement of the adrenal glands in treated females. Histopathological examination revealed swelling and single cell necrosis of the liver cells in both sexes given 200 mg/kg. Moreover, mitosis of the liver cells was observed in males given 200 mg/kg. The slight increase in the incidence of hyaline droplets of the renal tubules in males and basophilic changes of the renal tubules in females, both given 200 mg/kg, were also noted in a few females given 8 mg/kg or more, and necrosis of the renal tubules was observed in a few females given 40 and 200 mg/kg. A variety of lesions including a moderate degree of pigment deposit in the spleen, atrophy of the thymus, swelling of the liver cells, ulcer action in the stomach, duodenum and large intestine, single liver cell necrosis and fibrosis of the renal tubular epitherum were observed in females that delivered all stillborn pups and females where pups all died, in the group given 200 mg/kg. Counting numbers of spermatogenic cells at stage VIII in the testes from control males and males given 200 mg/kg revealed no treatment-related effects.

The NOEL for repeated dose toxicity was considered to be < 8 mg/kg/day.

3.1.3 Mutagenicity

In vitro Studies

Bacterial test

2,4-Dichloronitrobenzene showed positive results in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 at concentrations up to 0.215 mg/plate with or without a metabolic activation system (Haworth, 1983).

Non-bacterial test

A chromosomal aberration test in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guideline 473 was conducted using cultured Chinese Hamster lung (CHL/IU) cells. This study was well controlled and regarded as a key study.

No structural chromosomal aberrations or polyproidy were recognized up to a maximum concentration of 0.14 mg/ml under conditions of both continuous treatment and short-term treatment with or without an exogeneous metabolic activation system (MHW, 1996).

In vivo Studies

No data are available on *in vivo* genotoxic effects.

3.1.4 Toxicity for Reproduction

2,4-Dichloronitrobenzene was studied for oral toxicity in rats according to the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422] at doses of 0, 8, 40 and 200 mg/kg/day.

2,4-Dichloronitrobenzene showed no effects on mating, fertility or the estrus cycle. One female given 200 mg/kg died during delivery. All pups were stillborn with two females and pups died during the lactation period with three females given 200 mg/kg. In addition, the number of live pups born decreased, and number of stillborn pups tended to increase. The live birth index, viability index of pups at day 4 after birth and delivery index were decreased or showed a tendency for decrease in the same group, suggesting functional disturbances in delivery or lactation caused by the test substance. The NOEL for reproductive toxicity was considered to be 40 mg/kg/day for parental animals and offspring.

3.2 Initial Assessment for Human Health

2,4-Dichloronitrobenzene is produced in a closed system and is used as an intermediate in industry. As this chemical is not taken out from the vessel, the only situation that could lead to occupational exposure is when workers maintain the reaction vessel under local exhaust ventilation. Although there is no actual exposure data, using the physical-chemical properties of the substance and the EUSES model, exposure levels were calculated as 0 - 0.1 ppm for inhalation and 0 - 0.1 $mg/cm^2/day$ for the dermal route. However workers wear personal protective equipment (e.g. chemical cartridge respirator with an organic vapour cartridge) during the filling process. Therefore, the exposure at the work place is considered to be negligible for the current situation. In addition, this chemical is not contained in consumer products, because it is an intermediate in industrial use.

Although a positive result was obtained from an Ames test, the chemical showed no genotoxic effect in a chromosomal aberration test *in vitro*. In an OECD combined repeated dose and reproductive/developmental toxicity test, moderate effects to liver (e.g. increased liver weight and necrosis) and kidney (e.g. increased kidney weight and basophilic changes in the renal tubules) were observed at the middle dose (40 mg/kg/day). Similar slight effects to kidney were also seen in female at the lowest dose (8 mg/kg/day). Therefore, NOEL was strictly considered to be less than 8 mg/kg/day. Regarding reproductive/developmental toxicity, the chemical did not show any effects on mating fertility or estrous cycle. However, all pups of two females were stillborn, and during the lactation period, pups of three females died at the highest dose (200 mg/kg/day). In addition, functional disturbances in delivery or lactation caused by the test substance was expected. The NOEL for reproductive toxicity was 40 mg/kg/day for parental animals and offspring.

For human health, NOEL is estimated as less than 8 mg/kg/day for repeated dose and 40 mg/kg/day for reproductive toxicity. Regarding indirect exposure via environment, the daily intake through drinking water is estimated to be les than 9.0×10^{-10} mg/kg/day. The margin of safety is very large. Therefore, health risk through the environment, in general, is considered to be presumably low due to its use pattern and exposure situation.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

2,4-Dichloronitrobenzene has been tested in a limited number of aquatic species (*Selenastrum capricornutum*, *Daphnia magna* and *Oryzias latipes*), under OECD test guidelines [OECD TG 201, 202, 203,]. Acute and chronic toxicity data to test organisms for 2,4-dichloronitrobenzene are summarized in Table 3. No other ecotoxicological data are available.

Various NOEC and LC_{50} values were gained from above tests; 96h LC_{50} = 13 mg/l (acute fish); 24h EC_{50} = 12 mg/l (acute daphnia); 72h EC_{50} = 2.0 mg/l (acute algae); NOEC = 1.8 mg/L (algae), 21d NOEC = 0.056 mg/l (long-term daphnia reproduction). Therefore, the chemical is considered to be moderately toxic to fish, daphnids and algae. As the lowest chronic toxicity result, the 21 d-NOEC (reproduction) of *Daphnia magna* (0.056 mg/l), was adopted. As assessment factor of 100 is applied. Thus PNEC of 2,4-dichloronitrobenzene is 0.00056 mg/l. Since the PEC is lower than the PNEC, environmental risk is presumably low.

Table 3. Acute and chronic toxicity data of 2,4-dichloronitrobenzene to aquatic organisms.

Species	Endpoint[*1]	Conc. (mg/L)	Reference
Selenastrum capricornutum (algae)	Biomass: EC_{50} (72h) NOEC	2.0 mg/L 1.8 mg/L	EA, Japan. (1994)
Daphnia magna (water flea)	Imm: LC_{50} (24h) Imm: EC_{50} (21d) Rep: EC_{50} (21d) NOEC (21d)	12 mg/L > 0.56 mg/L 1.0 mg/L 0.056 mg/L	
Oryzias latipes (fish, Medaka)	Mor: LC_{50} (24h) Mor: LC_{50} (72h) Mor: LC_{50} (96h)	21 mg/L 18 mg/L 13 mg/L	

Notes: [*1] Mor; mortality, Rep; reproduction, Imm; Immobility

4.2 Initial Assessment for the Environment

The production volume of 2,4-dichloronitrobenzene in Japan was less than 50 tonnes during 1990 - 1993, and 1,500 tonnes in Germany in 1990. This chemical is used as an intermediate for the synthesis of pigments, pesticides and medicinal drugs in industry in Japan. This chemical is stable in neutral, acidic or alkaline solutions, and is considered as “not readily biodegradable”.

The potential environmental distribution of 2,4-dichloronitrobenzene obtained from a generic fugacity model (Mackay level III) showed that the chemical will be distributed mainly to water and soil. The predicted environmental concentration (PEC_{local}) of this chemical was estimated to be 2.7 x 10^{-8} mg/l from a Japanese local exposure scenario.

For the environment, various NOEC and LC_{50} values were gained from test results; 96h LC_{50} = 13 mg/l (acute fish); 24h EC_{50} = 12 mg/l (acute daphnia); 72h EC_{50} = 2.0 mg/l (acute algae); NOEC = 1.8 mg/l (algae); 21d NOEC = 0.056 mg/l (long-term daphnia reproduction). As the lowest chronic toxicity result 21d-NOEC (reproduction) of *Daphnia magna* (0.056 mg/l) was adopted. The assessment factor of 100 was used to both acute and chronic toxicity data to determine PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the

PNEC of the chemical is 0.00056 mg/l in the present report. The PEC is lower than the PNEC, therefore the environmental risk is presumably low.

5 RECOMMENDATIONS

Although 2,4-dichloronitrobenzene showed strong toxicity to daphnia and genotoxicity in an Ames test, exposure is low in the sponsor country.

Unless further information on exposure in other Member countries presents evidence to the contrary, it is currently considered of low potential risk and low priority for further work.

6 REFERENCES

BUA Report 64; GDCh Advisory Committee on Existing Chemicals of Environmental Relevance, August 1991, Hirzel Verlag, ISBN 3-7776-0552-2

EA, Japan (1995) Environment Monitoring of Chemicals - Environmental Survey Report of F.Y. 1994 (Office of Health Studies, Environmental Health Department, EA, Japan)

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EA & MITI, Japan (1994) Unpublished Report on Exposure Estimation (HPV/SIDS Test conducted by EA and MITI, Japan)

ECDIN database (1994)

Haworth et al. (1983) Environ. Mutagen., 5.

Lyman, W.J, W. F. Reehl and D. H. Rosenblatt (1981) "Handbook of Chemical Property Estimation Method", McGraw Hill Book Co.

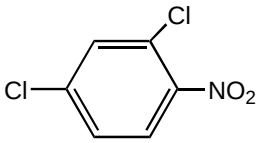
SIDS DOSSIER

Benzene, 2,4-dichloro-1-nitro-

CAS No. 611-06-3

Sponsor Country: Japan

S I D S P R O F I L E

1.01 A.	**CAS No.**	611-06-3
1.01 C.	**CHEMICAL NAME (OECD Name)**	Benzene, 2,4-dichloro-1-nitro-
1.01 D.	**CAS DESCRIPTOR**	Not applicable
1.01 G.	**STRUCTURAL FORMULA**	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	In Japan, 0.5 – 21 tonnes/year in 1992.
1.7	**USE PATTERN**	In Japan, Intermediates for pharmaceuticals, pesticides and pigments in closed system.
1.9	**SOURCES AND LEVELS OF EXPOSURE**	In Japan, 1. Amount released from production site to water is 1.4 kg/year All of the waste water is incinerated
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)		

SIDS SUMMARY

CAS NO: 611-06-6		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	Y	N	N	Y	N	Y	N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						Y
3.1.2	Stability in water	N						Y
3.2	Monitoring data	Y	N	N	Y	N	N	N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	Y						Y
3.6	Bioaccumulation	Y	Y	Y	N	N	Y	N
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	N						Y
4.2	Acute toxicity to Daphnia	N						Y
4.3	Toxicity to Algae	N						Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								
TOXICITY								
5.1.1	Acute Oral	Y	N	N	Y	N	Y	N
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	Y	N	N	Y	N	Y	N
5.4	Repeated Dose	N						Y
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	Y	N	N	Y	N	Y	N
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity *in vivo*	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	N						Y
5.11	Human experience	N						N
OTHER TOXICITY STUDIES RECEIVED								

1.01 SUBSTANCE INFORMATION

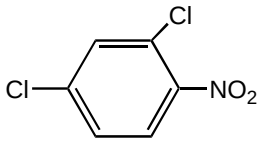
A. CAS Number 611-06-3

B. Name Benzene, 2,4-dichloro-1-nitro-

C. EINECS-Number

D. Molecular Formula $C_6H_3Cl_2NO_2$

E. Structural Formula



F. Molecular Weight 192.0

1.02 OECD INFORMATION

A. Sponsor Country: Japan

B. Lead Organization:
Name of Lead Organization:
Ministry of Health and Welfare (MHW)
Ministry of International Trade and Industry (MITI)
Environment Agency (EA)
Contact person: Mr. Yasuhisa Kawamura
Director
Second International Organization Bureau
Ministry of Foreign Affairs
Address: 2-2-1 Kasumigaseki, Chiyoda-ku
Tokyo 100, Japan
TEL 81-3-3581-0018
FAX 81-3-3503-3136

C. Name of responder

D. Name: **Same as above contact person**

Address:

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance
element **[ ]**; inorganic **[ ]**; natural substance **[ ]**;organic **[X]**; organometallic **[ ]**; petroleum product **[ ]**

B. Physical State
gaseous **[ ]**; liquid **[ ]**; solid **[X]**

C. Purity > 93 %

1.2 SYNONYMS 2,4-Dichloronitrobenzene

1.3 IMPURITIES 2,6-Dichloronitrobenzene

1.5 QUANTITY

Location	Production	Data
Japan	0.5 - 21 t/y	1988-1992
Germany	1,500 t/y	

Reference: MITI, Japan
ECDIN Database

1.7 USE PATTERN

A. General

Type of Use:	**Category:**
Industrial	Intermediates for medicinal drugs, pesticides and pigments

Reference: MITI, Japan

B. Uses in Consumer Products

None

Reference: MITI, Japan

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

None

1.9 SOURCES OF EXPOSURE

Source: Media of release: Water from a production site
Quantities per media: 1.4 kg/y

Reference: MITI, Japan

1.10 ADDITIONAL REMARKS

A. Options for disposal

Incineration

Reference: MITI, Japan

2.1 MELTING POINT

(a)
Value: 29-31 °C
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Data attached to reagent (Tokyo Kasai)

(b)
Value: 33 °C
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: BUA Report 64 (1991)

2.2 BOILING POINT

(a)
Value: 258 °C
Pressure: 1,013 hPa
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: BUA Report 64 (1991)

(b)
Value: 258.5°C
Pressure:
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: Lange's Handbook of Chemistry (11th edition)

2.3 DENSITY (Relative density)

Type: Bulk density **[ ]**; Density **[ ]**; Relative density **[X]**
Value: 1.54
Temperature: 15 °C
Method: calculated **[ ]**; measured **[X]**
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Reference: Company data (Hoechst)

2.4 VAPOUR PRESSURE

(a)
Value: 1.0 Pa
Temperature: 25°C
Method: calculated **[ ]**; measured **[X]**
OECD Test Guideline 104 Dynamic method

GLP: Yes **[X]** No **[ ]** ? **[ ]**
Reference: MITI, Japan (1994b)

(b)
Value: 0.0133 hPa
Temperature: 20 °C
Method: calculated **[X]**; measured **[ ]**
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Reference: BUA Report 64 (1991)

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

(a)
Log Pow: 2.90
Temperature: 25 °C
Method: calculated **[ ]**; measured **[X]**
OECD Test Guideline 107
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Reference: MITI, Japan (1994b)

(b)
Log Pow: 2.78 – 3.09
Temperature:
Method: calculated **[ ]**; measured **[X]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Reference: BUA Report 64 (1991)

2.6 WATER SOLUBILITY

A. Solubility

Value: 200 mg/l
Temperature: 25 °C
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[X]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**;
Not soluble **[ ]**
Method: OECD Test Guideline 105
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Reference: Unpublished Report (Test was performed in Chemicals Inspection and Testing Institute, Japan)

B. pH Value, pKa Value

No data available

2.7 FLASH POINT

No data available

2.8 AUTO FLAMMABILITY

No data available

2.9 FLAMMABILITY

No data available

2.10 EXPLOSIVE PROPERTIES

No data available

2.11 OXIDIZING PROPERTIES

No data available

2.12 OXIDATION: REDUCTION POTENTIAL

No data available

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

No data available

B. Other data

Henry constant: H = 1.36 $Pa/m^3/mol$

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type:	Air **[ ]**; Water **[X]**; Soil; Other **[ ]**	
Light source:	Sunlight **[X];** Xenon lamp **[ ];** Other **[ ]**	
Spectrum of substance:	epsilon = 1.93×10^{3} at 300 nm	
Estimated parameter for calculation:		
	Quantum yield	0.01
	Concentration	5×10^{-5} M
	Depth of water body	500 cm
	Conversion constant	6.023×10^{20}
Result:	Degradation rate	1.39×10^{-11} mol / l / s
	Half life	7.90×10^{-2} years
Reference:	W. J. Lyman, W. F. Reehl and D. H. Rosenblatt, "Handbook of Chemical Property Estimation Method", McGraw Hill Book Co., 1981.	

3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Result:	Stable at pH 4, 7 and 9 at 25 °C
Method:	OECD Test guideline 111
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	2,4-Dichloronitrobenzene
Reference:	Unpublished Report (Test was performed in Chemicals Inspection and Testing Institute, Japan)

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENT)

(a)

Type of Measurement:	Background **[ ]**, At contaminated Site **[ ]**; Other **[X]**
Media:	Surface water
Results:	ND (Detection limits: 0.06 ug/ml) in 27 areas in Japan in 1994.
Remarks:	None
Reference:	EA, Japan (1995)

(b)

Type of Measurement:	Background **[ ]**, At contaminated Site **[ ]**, Other **[X]**
Media:	Sediment
Results:	ND (detection limits: 0.0085 ug/g dry) in 27 areas in Japan in 1994.
Remarks:	None
Reference:	EA, Japan (1995)

(c)

Type of Measurement:	Background **[ ]**, At contaminated Site **[ ]**; Other **[X]**
Media:	fish
Results:	ND (Detection limits: 0.003 ug/g) in 27 areas in Japan in 1994
Remarks:	None
Reference:	EA, Japan (1995)

(d)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**, Other **[X]**
Media: air
Results: ND (Detection limits: 14 ng/m^3) in 27 areas in Japan in 1994.
Remarks: None
Reference: EA, Japan (1995)

(e)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**; Other **[X]**
Media: Surface water
Results: ND (Detection limits: 0.1 ug/l) in North Rhine-Westphalia in 1984 to 1989.
Remarks: None
Reference: BUA Report 64 (1991)

(f)
Type of Measurement: Background **[ ]**, At contaminated Site **[ ]**, Other **[X]**
Media: Surface water
Results: 1.0 ug/l (Maximum, Detection limits: unknown) in Main river in 1984 to 1989.
Remarks: None
Reference: BUA Report 64 (1991)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

No data available

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

The potential environmental distribution of 2,4-dichloronitrobenzene obtained from a generic level III fugacity model is shown in the table. The results show that if 2,4-dichloronitrobenzene is released mainly to soil or air, it is unlikely to distribute into other compartment. But, if 2,4-dichloronitrobenzene is released mainly to air, it is likely to be transported to soil.

Environmental distribution 2,4-dichloronitrobenzene using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	100% to soil Release:
Air	12.07 %	0.80 %	0.12 %
Water	7.86 %	91.79 %	2.80 %
Soil	79.89 %	5.28 %	97.02 %
Sediment	0.18 %	2.13 %	0.06 %

Reference: EA and MITI, Japan (1994)

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No data available

3.5 BIODEGRADATION

Type:	aerobic **[X]**; anaerobic **[ ]**
Inoculum:	adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical:	100 mg/l related to Test Substance **[X]**
Medium:	water**[ ];**water-sediment**[ ];**soil **[ ];**sewage treatment **[ ]** other **[** Japanese standard activated sludge **]**
Degradation:	Degree of degradation after 28 days 0, 0 and 0 % from BOD 6, 6 and 4 % from HPLC analysis
Results:	Readily biodeg. **[ ];** Inherently biodeg. **[ ]**; under test condition no biodegradation observed **[X]**
Method:	OECD Test Guideline 301 C
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	2,4-Dichloronitrobenzene
Reference:	MITI, Japan (1994b)

3.6 BOD_5,COD OR RATIO BOD_5/COD

Not applicable

3.7 BIOACCUMULATION

Species:	*Salmo gairdneri*
Exposure period:	36 days
Temperature:	
Concentration:	750 ng/l
BCF:	118
Method:	unknown
Type of test:	calculated **[ ]**; measured **[X]** static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other **[ ]**
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	2,4-dichloronitrobenzene
Remarks:	Biological half-life in fish (oral intake) is less than 3 days.
Reference:	BUA Report 64

3.8 ADDITIONAL REMARKS

A. Sewage treatment None

B. Other information None

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]** open-system **[X]**; closed-system **[ ]**
Species:	*Oryzias latipes*
Exposure period:	96 hr
Results:	LC_{50} (24h) = 21 mg/l (95% confidence limits: 18-25 mg/l) LC_{50} (48h) = 16 mg/l (95% confidence limits: 13-19 mg/l) LC_{50} (72h) = 18 mg/l (95% confidence limits: 13-18 mg/l) LC_{50} (96h) = 13 mg/l (95% confidence limits: 11-17 mg/l) NOEC = LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 203 (1981)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,4-Dichloronitrobenzene, purity = 99 %
Remarks:	A group of 10 fish were exposed to each of 5 nominal concentrations (5.6-56 mg/l). Stock solution was prepared with DMSO:HC 40 = 4:1 (100-1000 mg/l). Controls with and without this vehicle were taken for test.
Reference:	EA, Japan (1994)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
Exposure period:	24 hr
Results:	EC_{50} (24h) = 12 mg/l (95% confidence limits: 9.2-16 mg/l) EC_{50} (48h) = NOEC = LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 202 (1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,4-Dichloronitrobenzene, purity: = 99 %
Remarks:	20 daphnids (4 replicates; 5 organisms per replicate) were exposed to each of 5 nominal concentrations (5.6-56 mg/l). Stock solution was prepared with DMSO:HCO = 9:1(56-560 mg/l). Controls with and without this vehicle were taken for test.
Reference:	EA, Japan (1994)

B. Other aquatic organisms

No studies located

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

Species:	*Selenastrum capricornutum* ATCC 22662
End-point:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**
Exposure period:	72 hours

Results: Biomass: EC_{50} (24h) =
EC_{50} (72h) = 2.0 mg/l
NOEC = 1.8 mg/l ($p < 0.01$)
LOEC =
Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: open-system **[X]**; closed-system **[ ]**
OECD Test Guideline 201 (1984)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: 2,4-Dichloronitrobenzene, purity = 99 %
Remarks: The EC_{50} values for biomass were calculated based on 5 nominal concentrations (1.8-19 mg/l). Stock solution was prepared with DMSO (6.4 mg/l). Controls with and without this vehicle were taken for the test.
Reference: EA, Japan (1994)

4.4 TOXICITY TO BACTERIA

No studies located

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1. CHRONIC TOXICITY TO FISH

No studies located

4.5.2. CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

(a)
Type of test: static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]**;
open-system **[X]**; closed-system **[ ]**
Species: *Daphnia magna*
End-point: Mortality **[ ]**; Reproduction rate **[X]**; Other **[X]**
Exposure period: 21 day
Results:
Immobility: EC_{50} (48 h) = > 0.56 mg/l
EC_{50} (21 d) = > 0.56mg/l
NOEC =
LOEC =
Reproduction: EC_{50} (21 d) = 1.0 mg/l (95% confidence limits: 0.64-2.6 mg/l)
NOEC = 0.056 mg/l ($p < 0.05$)
LOEC = 0.1 mg/l ($p < 0.05$)
Analytical monitoring: Yes **[ ]** No **[X]** ? **[ ]**
Method: OECD Test Guideline 202 (1984)
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: 2,4-Dichloronitrobenzene, purity = 99 %
Remarks: 40 daphnids (4 replicates; 10 organisms per replicate) were exposed to each of 5 nominal concentrations (0.056-0.56 mg/l). Stock solution was prepared with DMSO:HCO-40=9:1(0.56-5.6 mg/l).
Controls with and without this vehicle were taken for test.
Reference: EA, Japan (1994)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data available

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data available

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No studies located

4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES

No data available

4.9 ADDITIONAL REMARKS

None

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type :	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value :	990 mg/kg
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	2,4-Dichloronitrobenzene, purity: unknown
Remarks:	None
Reference:	Company data (Japan)

(b)

Type :	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value :	379 mg/kg (male); 385 mg/kg (female)
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	2,4-Dichloronitrobenzene, purity: unknown
Remarks:	None
Reference:	Company data (Bayer AG)

5.1.2 ACUTE INHALATION TOXICITY

No data available

5.1.3 ACUTE DERMAL TOXICITY

Type :	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rabbit
Value:	921 mg/kg
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	2,4-Dichloronitrobenzene, purity: unknown
Remarks:	
Reference:	Company data (Hoechst AG, 1988)

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No data available

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Test species/strain:	Rabbit
Test method:	Patch test
GLP:	YES **[ ]** NO **[ ]** ? **[X]**
Test result:	Slightly irritating
Test substance:	2,4-Dichloronitrobenzene, purity: unknown
Remarks:	
Reference:	BUA Report 64 (1991)

5.2.2 EYE IRRITATION/CORROSION

Test species/strain: Rabbit
Test method: Unknown
GLP: YES **[ ]** NO **[ ]** ? **[X]**
Test result: Slightly irritating
Test substance: 2,4-Dichloronitrobenzene
Remarks:
Reference: BUA Report 64 (1991)

5.3 SKIN SENSITIZATION

No data available

5.4 REPEATED DOSE TOXICITY

Species/strain: Rat (Crj:CD(SD))
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral gavage
Exposure period: Males: 45 days including 14 days before mating
Females: from 14 days before mating to day 3 of lactation
Frequency of treatment: 7 days/week
Post exposure observation period:
Dose: 0, 8, 40 or 200 mg/kg (12 animals /group)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL: < 8 mg/kg/day
LOEL: 8 mg/kg/day
Results: One female rat given 200 mg/kg died during delivery, but no abnormal clinical signs were observed. The body weight gain of females given 200 mg/kg was lower than that controls during the gestation period. Hematological examination revealed decreases in red blood cells in males given 8 mg/kg or more groups, decreases in hematocrit and hemoglobin, increases in reticulocytes, and alight anemia in males given 40 and 200 mg/kg. Blood clinical examination revealed increases total protein, albumin and gamma-GTP, and decreases in creatinine in males given 40 and 200 mg/kg. Total bilirubin and A/G ratio were increased in males given 200 mg/kg. Absolute and relative liver and kidney weights showed increase in both sexes given 200 mg/kg. Necropsy revealed enlargement of the liver in both sexes given 200 mg/kg, and enlargement of the kidneys in male 200 mg/kg group. Other treatment related gross findings included atrophy of the thymus and enlargement of the adrenal glands in treated females. Histopathological examination revealed swelling and single cell necrosis of the liver cells in both sexes given 200 mg/kg. Moreover, mitosis of the liver cells were observed in males given 200 mg/kg. The slight increase in the incidence of hyaline droplets of the renal tubules in males and basophilic changes of the renal tubules in females, both given 200 mg/kg, were also noted in a few females given 8 mg/kg or more, and necrosis of the renal tubules was observed in a few females given 40 and 200 mg/kg. A variety of lesions including a moderate degree of pigment deposit in the spleen, atrophy of the thymus, swelling of the liver cells, ulcer action in the stomach, duodenum and large intestine, single liver cell necrosis and fibrosis of the

renal tubular epitherum were observed in females that delivered all stillborn pups and females where pups all died, in the group given 200 mg/kg. Counting numbers of spermatogenic cells at stage VIII in the testes from control males and males given 200 mg/kg revealed no treatment-related effects.

Method: OECD Combined Repeat dose and reproductive/ developmental Screening Toxicity Test (1992))
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Commercial, purity: > 98.0 %
Reference: MHW, Japan (1996)

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

(a)
Type: Bacterial reverse mutation assay
System of testing:
Species/strain: *S. typhimurium* TA 98, TA 100, TA 1535, TA1537
E. coli WP2 uvrA
Concentration: 0, 3.3, 10, 33, 100, 215 µg/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**;No data**[ ]**
Results:
Cytotoxicity conc: With metabolic activation:
Without metabolic activation:
Precipitation conc:
Genotoxic effects:

S. typhimurium TA98, TA 100, TA1535, TA1537

	+	?	-
With metabolic activation:	**[X]**	**[ ]**	**[ ]**
Without metabolic activation:	**[X]**	**[ ]**	**[ ]**

Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Teat substance: Commercial, purity: unknown
Remarks: Procedure: Plate incorporation method
Media:Histidine selective
Reference: Howorth et al., (1983)

B. NON-BACTERIAL IN VITRO TEST

Type : Cytogenetics Assay
System of testing:
Species/strain: Chinese hamster lung (CHL/IU) cells
Concentration: -S9 (continuous treatment) 0, 0.04, 0.07, 0.14 mg/ml
-S9 (short-term treatment) 0, 0.04, 0.07, 0.14 mg/ml
+S9 (short-term treatment) 0, 0.04, 0.07, 0.14 mg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**;
No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation:
Without metabolic activation:
Precipitation conc:

Genotoxic effects: + ? -
With metabolic activation: **[ ] [ ] [X]**
Without metabolic activation: **[ ] [ ] [X]**
Method: Japanese Guideline for Screening Mutagenicity testing of chemicals
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Commercial, purity 99.6 %
Remarks: Plates/test: 2
Activation system: S-9 fraction from the liver of
Phenobarbital and 5,6-Benzoflavone
Induced male SD derived rats with
NADPH-generating system
Media: RPMI 1640 medium *plus* 10% foetal calf serum
plus phytohaemagglutinin
No. replicates: 1
Reference: MHW, Japan (1996)

5.6 GENETIC TOXICITY IN VIVO

No data available

5.7 CARCINOGENICITY

No data available

5.8 TOXICITY TO REPRODUCTION

Type: Fertility **[ ]**; One generation study **[ ]**; Two generation study **[ ]**; Other **[X]**
Species/strain: Rat Crj:CD(SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: Males: 45 days
Females: from 14 days before mating to day 3 of lactation.
Frequency of treatment: 7 days/week
Postexposure observation period:
Premating exposure period: male: 14 days, female: 14 days
Duration of the test;
Doses: 0, 8, 40 or 200 mg/kg (12 animals/sex/group)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; Corn oil
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**;
Historical **[ ]**
NOEL Parental : 40 mg/kg/day
NOEL F1 Offspring: 40 mg/kg/day
NOEL F2 Offspring: N/A
Results: 2,4-Dichloronitrobenzene showed no effects on mating, fertility or the estrus cycle. One female given 200 mg/kg died during delivery. All pups were stillborn with two females and pups died during the lactation period with three females given 200 mg/kg. In addition, the number of live pups born decreased, and number of stillborn pups tended to increase. The live birth index, viability index of pups at day 4 after birth and delivery index were decreased or showed a tendency for decrease in the same group,

suggesting functional disturbances in delivery or lactation caused by the test substance.

Method: OECD Combined Repeat dose and reproductive/ developmental Screening Toxicity Test (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: > 98.0 %
Remarks:
Reference: MHW, Japan (1996)

5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

See 5.8

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No data available

B. Toxicodynamics, toxicokinetics

No data available

5.11 EXPERIENCE WITH HUMAN EXPOSURE

None

BUA Report 64; GDCh Advisory Committee on Existing Chemicals of Environmental Relevance, August 1991, Hirzel Verlag, ISBN 3-7776-0552-2

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